PCT/EP2004/003514

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

REC'D 21 MAY 2004
WIPO PCT

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

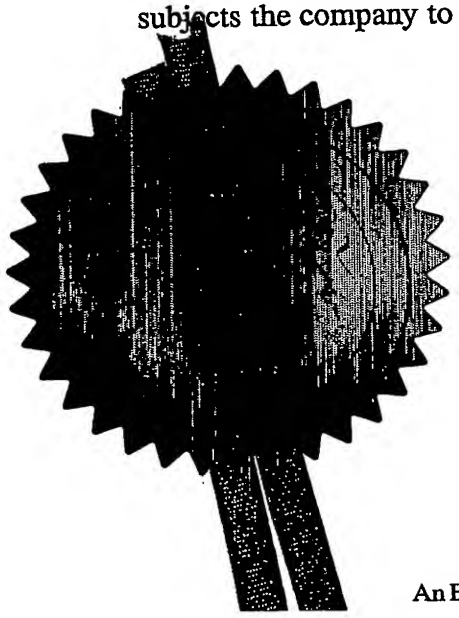
I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

I also certify that the attached copy of the request for grant of a Patent (Form 1/77) bears an amendment, effected by this office, following a request by the applicant and agreed to by the Comptroller-General.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed

Dated 12 February 2004

'atents Form 1/77

Patents Act 1977
(Rule 16)

THE PATENT OFFICE
04 APR 2003
RECEIVED BY HAND

The Patent Office

07APR03 E797994-17 D00524
P01/7700 0.00-0307867.2

1/77

Request for grant of a patent
(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office
Cardiff Road
Newport
Gwent NP10 8QQ

1.	Your reference	4-32805P1
2.	Patent application number *(The Patent Office will fill in this p*	0307867.2
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	NOVARTIS AG LICHTSTRASSE 35 4056 BASEL SWITZERLAND
	Patent ADP number *(if you know it)*	
	If the applicant is a corporate body, give the country/state of its incorporation	SWITZERLAND
4.	Title of invention	Pharmaceutical Composition
5.	Novartis Pharmaceuticals UK Limited Patents and Trademarks Wimblehurst Road Horsham West Sussex RH12 5AB	B.A. YORKE & CO. CHARTERED PATENT AGENTS COOMB HOUSE, 7 ST. JOHN'S ROAD ISLEWORTH MIDDLESEX TW7 6NH 1800001

7125487605

16002 JPM 02/04.

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application		Number of earlier application	Date of filing (day/month/year)
8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *(see note (d))*	Yes		

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	9
Claim(s)	1
Abstract	1
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature: B.A Yorke & Co.

Date: 4th April 2003

B.A. Yorke & Co.

12. Name and daytime telephone number of person to contact in the United Kingdom

Mrs. S. Schnerr
020 8560 5847

Warning

After an application for a patent has been filed. the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the united Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) *If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.*

b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

d) *Once you have filled in the form you must remember to sign and date it.*

e) *For details of the fee and ways to pay please contact the Patent Office.*

PHARMACEUTICAL COMPOSITION

The invention relates to pharmaceutical compositions, for use in particular in the treatment of skin diseases. It concerns a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant and a ceramide.

It has now been found that, surprisingly, macrolide T-cell immunomodulators and immunosuppressants, when used in combination with ceramides, act synergistically, resulting in a potentiation of pharmacological activity, such that effective beneficial, especially anti-dermatitis activity is seen upon co-administration at dosages which would be well below the effective dosages administered individually.

The invention thus concerns novel pharmaceutical compositions comprising a **macrolide T-cell immunomodulator or immunosuppressant** in association or combination with a **ceramide**, hereinafter briefly named "the compositions of the invention".

A macrolide T-cell immunomodulator or immunosuppressant is to be understood herein as being a T-cell immunomodulator or T-cell immunosuppressant which has a macrocyclic compound structure including a lactone or lactam moiety. While it preferably has at least some T-cell immunomodulating or immunosuppressant activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as anti-inflammatory activity.

A ceramide is to be understood herein as being an N-acyl fatty acid derivative of a sphingosine (1,3-dihydroxy-2-amino-4-octadecene), or a derivative thereof, such as a glycosphingolipid, e.g. an N-acyl fatty acid derivative of a sphingosine where the acyl group is derived from a fatty acid of 18 to 26 carbon atoms. It may be a mixture of sphingosine or phytosphingosine derivatives, containing saturated or unsaturated acids, e.g. non-hydroxy-substituted or α-hydroxy- or ω-hydroxy-substituted. The term "ceramide" as used herein includes synthetic analogues of natural ceramides, e.g. as known under the term pseudoceramide.

The natural ceramides represent the most abundant group of stratum corneum lipids. They are structural lipids present in the intercellular spaces of the stratum corneum (J. Invest. Dermat. 87 [1986] 758-761).

The compositions of the invention may be adapted for systemic, e.g. oral or intravenous, or for topical use; preferably they are adapted for topical use. They are useful for the known indications of the particular active agents incorporated therein. They are particularly indicated for use in dermatological or mucosal diseases, e.g. dermatological or mucosal diseases which have an inflammatory component or involve inflammatory complications, such as atopic or contact dermatitis or dry skin, asteatotic eczema and xerosis, and for restorement of the lipid skin barrier in the stratum corneum.

Oral administration of essential unsaturated fatty acids such as linoleic acid has been shown to have a beneficial effect in atopic dermatitis patients, presumably by restoration of functional ceramides (B. Melnik et al., Br. J. Dermatol. 119 [1988] 547-548).

A suitable **macrolide T-cell immunomodulator or immunosuppressant** is for example an FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor, in particular an **asco-** or **rapamycin**. It preferably is an ascomycin. While the macrolide preferably has at least some calcineurin- or mitogen-activated kinase modulating or inhibiting activity, it may also exhibit concomitantly or predominantly further pharmaceutical properties, such as antiinflammatory activity. It preferably is a compound, e.g. an ascomycin, having rather long-acting activity relatively to other members of the same structural class, e.g. it is metabolically degraded slowly to inactive products.

An asco- or rapamycin is to be understood as asco- or rapamycin as such, or a derivative thereof. A derivative is to be understood as being an antagonist, agonist or analogue of the parent compound which retains the basic structure and modulates at least one of the biological, for example immunological properties of the parent compound.

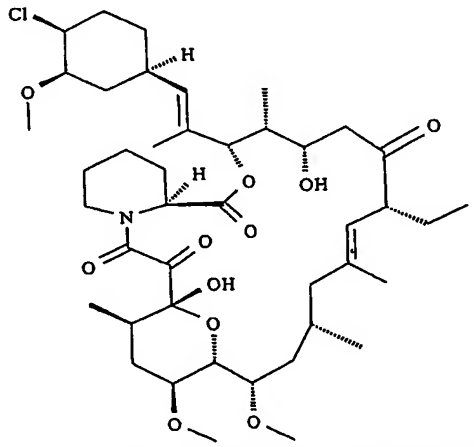
Suitable **ascomycins** are e.g. as described in EP 184162, EP 315978, EP 323042, EP 423714, EP 427680, EP 465426, EP 474126, WO 91/13889, WO 91/19495, EP 484936, EP 523088, EP 532089, EP 569337, EP 626385, WO 93/5059 and WO 97/8182;
in particular:

- **ascomycin**;
- **tacrolimus** (FK506; Prograf^{R});
- **imidazolylmethoxyascomycin** (WO 97/8182 in Example 1 and as compound of formula I);

- **32-O-(1-hydroxyethylindol-5-yl)ascomycin** (L-732531) (Transplantation 65 [1998] 10-18, 18-26, on page 11, Figure 1; and
- **(32-desoxy,32-epi-N1-tetrazolyl)ascomycin** (ABT-281) (J.Invest.Dermatol. 12 [1999] 729-738, on page 730, Figure 1); preferably:
- {1R,5Z,9S,12S-[1E-(1R,3R,4R)],13R,14S,17R,18E,21S,23S,24R,25S,27R}-17-ethyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0(4,9)]octacos-5,18-diene-2,3,10,16-tetraone (Example 8 in EP 626385), hereinafter referred to as "**5,6-dehydroascomycin**";
- {1E-(1R,3R,4R)]1R,4S,5R,6S,9R,10E,13S,15S,16R,17S,19S,20S}-9-ethyl-6,16,20-trihydroxy-4-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-15,17-dimethoxy-5,11,13,19-tetramethyl-3-oxa-22-azatricyclo[18.6.1.0(1,22)]heptacos-10-ene-2,8,21,27-tetraone (Examples 6d and 71 in EP 569337), hereinafter referred to as "**ASD 732**";

and especially

- **pimecrolimus** (INN recommended) (ASM981; Elidel™), i.e. {[1E-(1R,3R,4S)]1R,9S,12S, 13R,14S,17R,18E, 21S,23S,24R,25S,27R}-12-[2-(4-chloro-3-methoxycyclohexyl)-1-methylvinyl]-17-ethyl-1,14-dihydroxy-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28,dioxa-4-azatricyclo [22.3.1.0(4,9)]octacos-18-ene-2,3,10,16-tetraone, of formula I



(Example 66a in EP 427680), hereinafter referred to as "**33-epichloro-33-desoxyascomycin**".

Suitable **rapamycins** are e.g. as described in USP 3'929'992, WO 94/9010 and USP 5'258'389, preferably **sirolimus** (rapamycin; Rapamune®) and **everolimus** (RAD001; Certican®).

A suitable **ceramide** is for example:

- a natural ceramide, e.g. as described in J. Invest. dermatol. 84 (1985) 410-412, e.g. ceramide 3 [M. Kerscher et al., Eur. J. Dermatology 1 [1991] 39-43; S.A. Long et al., Arch. Dermatol. Res. 277 (1985) 284-287];
- a pseudoceramide (Eur. J. Dermatology 1 [1991] 39-43; J. Clin. Invest. 94 [1994] 89-96), e.g. A-pseudoceramide, or PC-9S (20th World Congress of Dermatology, Paris [July 1-5, 2002], Book II, Poster Abstracts, Abstr. 228, p. 1S, 415);
- a ceramide-based barrier repair agent such as TriCeram^{R} [which contains 2.1 % ceramides, 0.8 % free fatty acids and 0.8 % cholesterol by weight in an oil-in-water vehicle comprising lanolin];

or another agent that contains ceramide or pseudoceramide or that influences ceramide homeostase, e.g. an agent that stimulates ceramide synthesis, such as a ceramide precursor, e.g. an essential unsaturated fatty acid such as linoleic acid, or that inhibits ceramide degradation by e.g. ceramidases (ceramide inhibitor);

preferably ceramide 3, PC-9S or linoleic acid.

Preferred for use in the treatment of conditions where inflammation is involved are compositions of the invention wherein one or both components possess some degree of inherent anti-inflammatory activity. Particularly preferred are compositions comprising an ascomycin in combination with a ceramide, especially 33-epichloro-33-desoxyascomycin in combination with ceramide 3, PC-9S or linoleic acid. The inflammatory condition is e.g. atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis.

"Treatment" as used herein includes prevention, namely prophylactic as well as curative treatment.

Synergy is e.g. calculated as described in Berenbaum, Clin. Exp. Immunol. 28 (1977) 1, using an interaction term to correct for differences in mechanism between the two drugs, as described in Chou et al., Transpl. Proc. 26 (1994) 3043. The index of synergy is calculated as:

$$\frac{\text{dose of A}}{A_E} + \frac{\text{dose of B}}{B_E} + \frac{\text{(dose of A) x (dose of B)}}{A_E \times B_E}$$

in which the doses of the compounds A and B represent those used in a particular combination, and A_E and B_E are the individual doses of A and B respectively giving the same effect. If the result is less than 1, there is synergy; if the result is 1, the effect is additive; if the result is greater than 1, A and B are antagonistic. By plotting an isobologram of dose of A / A_E vs. dose of B / B_E the combination of maximum synergy can be determined. The synergistic ratio expressed in terms of the ratio by weight of the two compositions at synergistic amounts along the isobologram, especially at or near the point of maximum synergy, can then be used to determine formulations containing an optimally synergistic ratio of the two compounds.

Activity may e.g. be determined in known assay models for testing the activity of the individual components of the compositions.

The invention also provides products and methods for co-administration of a macrolide T-cell immunomodulator or immunosuppressant, e.g. 33-epichloro-33-desoxy-ascomycin or 5,6-dehydroascomycin, and a ceramide, e.g. ceramide 3, PC-9S or linoleic acid, at synergistically effective dosages, e.g.:

- a method of treatment or prevention of a dermatological or mucosal disease such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis in a subject suffering from or at risk for such condition, comprising co-administering synergistically effective amounts of a composition of the invention;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a medicament for co-administration in synergistically effective amounts with a ceramide;
- the use of a ceramide in the manufacture of a medicament for co-administration in synergistically effective amounts with a macrolide T-cell immunomodulator or immunosuppressant;
- a kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and a ceramide in separate unit dosage forms, preferably wherein the unit dosage forms are suitable for administration of the component compounds in synergistically effective amounts, together with instruction for use, optionally with further means for facilitating compliance with the administration of the component compounds, e.g. a label or drawings;
- the use of a macrolide T-cell immunomodulator or immunosuppressant in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a ceramide;

- the use of a ceramide in the manufacture of a pharmaceutical kit which is to be used for facilitating co-administration with a macrolide T-cell immunomodulator or immunosuppressant;
- a macrolide T-cell immunomodulator or immunosuppressant and a ceramide as a combined pharmaceutical preparation for simultaneous, separate or sequential use, preferably in synergistically effective amounts, e.g. for the treatment or prevention of a dermatological or mucosal disease such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis;
- a pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with a ceramide, e.g. in synergistically effective amounts, together with at least one pharmaceutically acceptable diluent or carrier, e.g. for use in treatment or prevention of a dermatological or mucosal disease such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis; and
- a process for the preparation of a composition of the invention comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and a ceramide, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

Synergistic activity may be determined e.g. in a rat model of essential acid-deficient diet-induced dermatitis, e.g. as described in G. Imokawa et al., J. Clin. Invest. 94 (1994) 89-96.

By "synergistically effective amounts" is meant an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of ceramide which are individually below their respective effective dosages for a relevant indication, but which are pharmaceutically active on co-administration, e.g. in a synergistic ratio, for example as calculated above. Furthermore, "synergistically effective amounts" may mean an amount of macrolide T-cell immunomodulator or immunosuppressant and an amount of ceramide which are individually equal to their respective effective dosages for a relevant indication, and which result in a more than additive effect.

The molar amount of macrolide T-cell immunomodulator or immunosuppressant present is from roughly similar to, to significantly less than the amount of ceramide, preferably half as much or less. Synergistic ratios of macrolide T-cell immunomodulator or immunosuppressant to ceramide by weight are thus suitably from about 10:1 to about 1:50,

preferably from about 5:1 to about 1:20, most preferably from about 1:1 to about 1:15, e.g. about 1:12.

The compositions of the invention can be administered as a free combination, or can be formulated into a fixed combination, which greatly enhances the convenience for the patient.

Absolute dosages of the compounds will vary depending on a number of factors, e.g. the individual, the route of administration, the desired duration, the rate of release of the active agent and the nature and severity of the condition to be treated. For example, the amount of active agents required and the release rate thereof may be determined on the basis of known in vitro and in vivo techniques, determining how long a particular active agent concentration in the blood plasma remains at an acceptable level for a therapeutic effect.

For example, in prevention and treatment of a dermatological or mucosal disease such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis, an initial dosage of about 2-3 times the maintenance dosage is suitably administered, followed by a daily dosage of about 2-3 times the maintenance dosage for a period of from one to two weeks, and subsequently the dose is gradually tapered down at a rate of about 5 % per week to reach the maintenance dosage. In general, synergistically effective amounts of 33-epichloro-33-desoxyascomycin and ceramide, e.g. ceramide 3, PC-9S or linoleic acid, on oral administration for use in prevention and treatment of atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis in larger animals, e.g. man, are amounts of 33-epichloro-33-desoxyascomycin of up to about 2 mg/kg/day, e.g. from about 0.01 mg/kg/day to about 2 mg/kg/day, preferably about 0.5 mg/kg/day, in combination or co-administration with amounts of ceramide, such as ceramide 3, PC-9S or linoleic acid of up to about 50 mg/kg/day, e.g. from about 0.25 mg/kg/day to about 50 mg/kg/day, preferably about 2.5 mg/kg/day, in a synergistic ratio, as described. Suitable unit dosage forms for oral co-administration of these compounds thus may contain on the order of from about 0.5 mg to about 100 mg, preferably about 3 mg to about 30 mg of 33-epichloro-33-desoxyascomycin, and from about 10 mg to about 3000 mg, preferably about 50 mg to about 500 mg of ceramide. The daily dosage for oral administration is preferably taken in a single dose, but may be spread

out over two, three or four dosages per day. For i.v. administration, the effective dosage is lower than that required for oral administration, e.g. about one fifth the oral dosage.

By "co-administration" is meant administration of the components of the compositions of the invention together or at substantially the same time, e.g. within fifteen minutes or less, either in the same vehicle or in separate vehicles, so that upon oral administration, for example, both compounds are present simultaneously in the gastrointestinal tract. Preferably, the compounds are administered as a fixed combination.

The compositions of the invention include compositions suitable for administration by any conventional route, in particular compositions suitable for administration either enterally, for example, orally, e.g. in the form of solutions for drinking, tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions; or topically, e.g. for the treatment of inflammatory conditions of the skin or mucosae, e.g. in the form of a dermal cream, ointment, ear drops, mousse, shampoo, solution, lotion, gel, emulgel or like preparation, e.g. in a concentration of from about 0.1 % to about 10 % by weight of each component, especially in combination or association with penetration enhancing agents, as well as for application to the eye, e.g. in the form of an ocular cream, gel or eye-drop preparation, for treatment of inflammatory conditions of the lungs and airways, e.g. in the form of inhalable compositions, and for mucosal application, e.g. in the form of vaginal tablets.

The compositions of the invention are suitably emulsions, microemulsions, emulsion preconcentrates or microemulsion preconcentrates, or solid dispersions, especially water-in-oil microemulsion preconcentrates or oil-in-water microemulsions, comprising the macrolide T-cell immunomodulator or immunosuppressant and the ceramide in a synergistic ratio.

The compositions of the invention can be prepared in conventional manner, e.g. by mixing a macrolide T-cell immunomodulator or immunosuppressant and a ceramide, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

The active agent components may be in free form or pharmaceutically acceptable salt form as appropriate.

The following Example illustrates the invention. The compounds are in free, i.e. neutral or base form unless specified otherwise.

Example: Cream

Component	Amount (g)
33-Epichloro-33-desoxyascomycin	1.00
Ceramide 3	1.00
Triglycerides, medium chain	15.00
Oleyl alcohol	10.00
Sodium cetylstearyl sulfate	1.00
Cetyl alcohol	4.00
Stearyl alcohol	4.00
Glyceryl monostearate	2.00
Benzyl alcohol	1.00
Propylene glycol	5.00
Citric acid	0.05
Sodium hydroxide	*
Water	ad 100.0

* amount required to adjust pH to 5.5

The preparation follows the conventional manufacturing procedures for an emulsion. The ascomycin and the ceramide are added to the heated homogeneous oily phase which contains triglycerides medium chain, oleyl alcohol, sodium cetylstearyl sulfate, cetyl alcohol , stearyl alcohol and glyceryl monostearate. In parallel, the water phase containing benzyl alcohol, propylene glycol, citric acid and sodium hydroxide is heated at the same temperature as the oily phase. The oily phase is added to the water phase and homogeneisation is performed. The resultant cream is cooled to room temperature.

Claims:

1. A pharmaceutical composition comprising a macrolide T-cell immunomodulator or immunosuppressant in combination or association with a ceramide, together with at least one pharmaceutically acceptable diluent or carrier.

2. A composition according to claim 1 comprising 33-epichloro-33-desoxyascomycin in combination or association with ceramide 3, PC-9S or linoleic acid.

3. A method of treatment of a dermatological or mucosal disease such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis in a subject suffering from or at risk for such condition, comprising co-administering a synergistically effective amount of a composition according to claim 1.

4. A process for the preparation of a composition according to claim 1 comprising mixing a macrolide T-cell immunomodulator or immunosuppressant and a ceramide, in combination or association with at least one pharmaceutically acceptable diluent or carrier.

5. A kit of parts comprising a macrolide T-cell immunomodulator or immunosuppressant and a ceramide in separate unit dosage forms, together with instructions for use.

Abstract:

PHARMACEUTICAL COMPOSITION

Synergistic combinations of a macrolide T-cell immunomodulator or immunosuppressant such as 33-epichloro-33-desoxyascomycin and a ceramide such as ceramide 3, PC-9S or linoleic acid are provided, which are useful in particular in the treatment of dermatological or mucosal diseases such as atopic or contact dermatitis or dry skin, asteatotic eczema or xerosis.